PATENT SPECIFICATION

768,821

Date of Application and filing Complete Specification: April 29, 1955.
No. 12476/55.
Application made in Germany on May 17, 1954.
Complete Specification Published: Feb. 20, 1957.

Index at acceptance:—Class 2(3), C3A14C.
International Classification:—C07d.

COMPLETE SPECIFICATION

ERRATA

SPECIFICATION No. 768,821

Page 1, line 16, *for* " phenol " *read* " phenyl "
Page 2, line 29, *for* " anhydric " *read* " anhydride "
Page 2, line 67, *for* " dioxo-piperidine " *read* " dioxopiperidine "

THE PATENT OFFICE
10th June, 1960

wherein R represents hydrogen, an aliphatic radical which contains 1 to 6 carbon atoms, a phenol radical or a benzyl radical and X represents the radical of the imide of a dicarboxylic acid attached to the piperidine ring by the imido nitrogen atom.

The aliphatic radicals of the substituent R may be saturated or unsaturated. The imides of dicarboxylic acids may be imides of dicarboxylic acids of the aliphatic, cycloaliphatic, aromatic or heterocyclic series. It is advantageous to employ the imides of phthalic acid and succinic acid.

According to one preferred form of the present invention, X stands for the phthalimide radical and R for an aliphatic radical with 1 to 6 carbon atoms, a phenyl radical or a benzyl radical.

The products of the invention possess valuable therapeutic properties. They cause a strongly pronounced lowering of the motility, i.e. the phenomenon of motion, and have a

manner that water is split off and the ring is closed. Instead of using the dicarboxylic acid, it is also possible to employ functional derivatives thereof, such as acid halides, acid esters and acid amides.

The proportions of the components used for the ring formation are advantageously such that at least 1 mol of the compound yielding the nitrogen imide is used to one mol of the acid component.

The invention is illustrated by the following examples:

EXAMPLE 1.

27.7 Gm. of N-phthalyl glutamic acid are mixed with 66 gm. of a 33% solution of ethylamine in water and slowly heated in an oil bath to 160—180°C., the mixture being maintained at this temperature for 15 to 20 minutes. The reaction product, 1-ethyl-3-phthalimido-2,6-dioxopiperidine, is recrystallised from alcohol by fractionation. It melts at 209°C. The DL 50 (50% lethal dose) is higher than 120 mg/20 gm of mouse, while the therapeutic dose is 10 mg/20 gm. of mouse.

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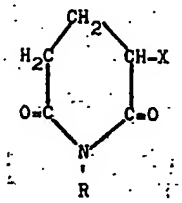
COMPLETE SPECIFICATION

Novel Products of the Amino-Piperidine-2,6-Dione Series

We, CHEMIE GRÜNENTHAL GMBH, Stolberg im Rheinland, Germany, a Body Corporate organised under the Laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel products of the amino-piperidine-2,6-dione series.

The novel products of the invention have the general formula



wherein R represents hydrogen, an aliphatic radical which contains 1 to 6 carbon atoms, a phenol radical or a benzyl radical and X represents the radical of the imide of a dicarboxylic acid attached to the piperidine ring by the imido nitrogen atom.

The aliphatic radicals of the substituent R may be saturated or unsaturated. The imides of dicarboxylic acids may be imides of dicarboxylic acids of the aliphatic, cycloaliphatic, aromatic or heterocyclic series. It is advantageous to employ the imides of phthalic acid and succinic acid.

According to one preferred form of the present invention, X stands for the phthalimide radical and R for an aliphatic radical with 1 to 6 carbon atoms, a phenyl radical or a benzyl radical.

The products of the invention possess valuable therapeutic properties. They cause a strongly pronounced lowering of the motility, i.e. the phenomenon of motion, and have a very low toxicity. They may be generally employed for "central attenuation" (vegetative dystonia). The products of the invention do not have any peripherally paralysing curare-like effects. In addition, the compounds have certain spasmolytic and antihistominic effects. Dispensed in larger quantities, the products of the invention, and particularly 3-phthalimido-2,6-dioxopiperidine are effective as soporifics. The products are fully effective, both when used parenterally or orally.

The novel products may be produced by reacting an aliphatic dicarboxylic acid which contains 5 C-atoms in a straight chain, and the α-methylene group of which is substituted by the substituent X in accordance with the aforementioned general formula, with urea or a substitution product thereof or with a primary amine or an acid amide in such manner that water is split off and the ring is closed. Instead of using the dicarboxylic acid, it is also possible to employ functional derivatives thereof, such as acid halides, acid esters and acid amides.

The proportions of the components used for the ring formation are advantageously such that at least 1 mol of the compound yielding the nitrogen imide is used to one mol of the acid component.

The invention is illustrated by the following examples:

EXAMPLE 1.

27.7 Gm. of N-phthalyl glutamic acid are mixed with 66 gm. of a 33% solution of ethylamine in water and slowly heated in an oil bath to 160—180°C., the mixture being maintained at this temperature for 15 to 20 minutes. The reaction product, 1-ethyl-3-phthalimido-2,6-dioxopiperidine, is recrystallised from alcohol by fractionation. It melts at 209°C. The DL 50 (50% lethal dose) is higher than 120 mg/20 gm of mouse, while the therapeutic dose is 10 mg/20 gm. of mouse.

EXAMPLE 2.

28.5 Gm. of N-succinyl-glutamic acid diethyl ester are heated for 30 minutes to 140—150°C. with 70 gm. of propylamine with addition of 5 gm. of sodium methylate. The product, 1-propyl-3-succinimido-2,6-dioxopiperidine, is purified as in Example 1 by fractional crystallisation.

EXAMPLE 3.

26 Gm. of N-phthalyl glutamic acid anhydride are melted with 12 gm. of urea in an oil bath at 170—180°C. until the reaction is completed, which takes about 20 minutes. The reaction takes place with violent evolution of carbon dioxide and ammonia. After cooling, the reaction product is recrystallised by fractionation from 95% alcohol, and the first fraction may contain phthalic acid derivatives. The required product, 3-phthalimido-2,6-dioxopiperidine, melts at 269—271°C. The substance is soluble in hot alcohol and in dimethyl formamide: it is also soluble in strong lyes, the solutions obtained having a yellowish colour. The yield is about 65—70% of the theoretical.

EXAMPLE 4.

Dry gaseous ammonia is introduced at about 180°C. into 13 gm. of molten N-phthalyl glutamic acid anhydric which is disposed in a loosely closed vessel, the process being so regulated that the water being formed is distilled off. A white substance simultaneously sublimes from the reaction mixture. After being cooled, the melt is worked up as in Example 3. The product which is obtained, 3-phthalimido-2,6-dioxopiperidine, melts at 269—271°C.

EXAMPLE 5.

13 Gm. of N-phthalyl glutamic acid anhydride are melted with 21.2 gm. of symmetrical diphenyl urea at 170—180°C. in an oil bath. The evolution of gas has practically been completed after about 20 minutes. After cooling, the aniline which is formed is first of all separated with a little ether. By fractional crystallisation from 95% alcohol, there are obtained a small amount of unchanged diphenyl urea, possibly phthalic acid derivatives, while the main quantity consists of 1-phenyl-3-phthalimido-2,6-dioxopiperidine with a melting point of 187°C.

EXAMPLE 6.

If gaseous ammonia is passed into phthalyl glutamic acid in an autoclave and if the latter is heated for a short time to 140—160°C., it is possible to isolate 3-phthalimido-2,6-dioxopiperidine. After recrystallisation by fractionation from 95% alcohol, the product melts at 269—271°C.

EXAMPLE 7.

13 Gm. of N-phthalyl glutamic acid anhydride are melted with 6 gm. of benzylamine at 180°C. for 15 minutes in an oil bath. After cooling, the reaction mixture is worked up by fractional crystallisation from 95% alcohol. 1-benzyl-3-phthalimido-2,6-dioxo-piperidine is obtained with the melting point of 104—108°C.

EXAMPLE 8.

13 Gm. of N-phthalyl glutamic acid anhydride are suspended in 100 cc. of absolute xylene and mixed with a solution of 6.4 gm. of benzylamine in 50 cc. of absolute xylene. This mixture is boiled under reflux for 4 hours on an oil bath. The xylene is then evaporated *in vacuo* and the residue recrystallised from 95% alcohol. The melting point of the product obtained 1-benzyl-3-phthalimido-2,6-dioxopiperidine, is 104—108°C. and the yield about 80% of the theoretical.

EXAMPLE 9.

The procedure indicated in Example 8 is followed, using 13.85 gm. of N-phthalyl glutamic acid. The same product is obtained.

EXAMPLE 10.

13 Gm. of phthalyl glutamic acid anhydride and 6 gm. of urea are heated to boiling point in 75 cc. of absolute xylene for 4 hours in an oil bath. Formation of a sublimate takes place with evolution of ammonia and carbon dioxide. The xylene is then distilled off *in vacuo* and the residue recrystallised from 95% alcohol by fractionation. In addition to some phthalimide and phthalyl glutamin, the required 3-phthalimido-2,6-dioxopiperidine is obtained, having a melting point of 269—271°C.

EXAMPLE 11.

The procedure is as in Example 10, but 14 gm. of phthalyl glutamic acid are used instead of phthalyl glutamic acid anhydride. The same product is obtained.

EXAMPLE 12.

The procedure is as in Example 10, but 7.6 gm. of thiourea are used instead of urea. The same product is obtained.

EXAMPLE 13.

The procedure is as in Example 12, but using 14 gm. of phthalyl glutamic acid instead of phthalyl glutamic acid anhydride. The same product, 3-phthalimido-2,6-dioxopiperidine, is obtained.

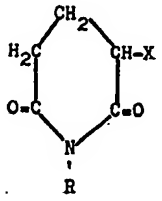
EXAMPLE 14.

13 Gm. of phthalyl glutamic acid anhydride and 5.7 gm. of allyl amine are heated in an oil bath to 175°C and maintained at this

temperature for about 15 minutes. After cooling, the reaction product is recrystallised by fractionation from aqueous alcohol. The product obtained, 1-allyl-3-phthalimido-2,6-dioxopiperidine, melts at 164—167°C.

What we claim is:—

1. New chemical compounds of the general formula



wherein R represents hydrogen, an aliphatic radical which contains 1 to 6 carbon atoms, a phenyl radical or a benzyl radical and X represents the radical of the imide of a dicarboxylic acid attached to the piperidine ring by the imido nitrogen atom.

2. 3-Phthalimido-2,6-dioxopiperidines in which the hydrogen atom on the piperidine nitrogen is substituted by an aliphatic radical with 1 to 6 carbon atoms, a phenyl radical or a benzyl radical.

3. 3-Phthalimido-2,6-dioxopiperidine.

4. New chemical compounds of the general formula specified in Claim 1, whenever produced by a process substantially as described with reference to any of the Examples.

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